LETTER TO THE EDITOR

COLORECTAL CANCER IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A SINGLE-CENTER EXPERIENCE

E. SINAGRA[1,2], V. GUARNOTTA[3], D. RAIMONDO[1], F. MOCCIARO[4], S. DOLCIMASCOLO[3], C.A. RIZZOLO[3], F. PUCCIA[3], N. MALTESE[3], R. CITARRELLA[3], M. MESSINA[5], M. SPADA[5], G. TOMASELLO[2,6], F. CAPPELLO[2,6], A. LEONE[7], F. ROSSI[1], R. DI MITRI[4], G.C. MORREALE[8], S. MARASÀ[9], M. MIDIRI[10], F. MIDIRI[10] and D. SINAGRA[3]

[1]Gastroenterology and Endoscopy Unit, Fondazione Istituto G. Giglio,Cefalù, Italy; [2]Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy; [3]Section of Cardio-Respiratory and Endocrine-Metabolic Diseases, Biomedical Department of Internal and Specialist Medicine (DIBIMIS), University of Palermo, Palermo, Italy; [4]Gastroenterology and Endoscopy Unit, ARNAS Civico-Di Cristina-Benfratelli Hospital, Palermo, Italy; [5]Oncology Unit, Fondazione Istituto G. Giglio, Cefalù, Italy; [6]Department of Experimental Biomedicine and Clinical Neuroscience, Section of Human Anatomy, University of Palermo, Palermo, Italy; [7]Department of Experimental Biomedicine and Clinical Neuroscience, Section of Histology, University of Palermo, Palermo, Italy; [8]Unit of Gastroenterology, Ospedali Riuniti Villa Sofia-Vincenzo Cervello, Palermo, Italy; [9]Centro Diagnostico Marasà, Palermo, Italy; [10]DIBIMED, Section of Radiology, University of Palermo, Palermo, Italy

Received April 26, 2017 – Accepted September 29, 2017

Abstract Type 2 diabetes mellitus (T2DM) is associated with an increased risk of colorectal cancer (CRC). The aim of the study is to evaluate the prevalence of CRC in a cohort of Caucasian patients with T2DM and the association with other variables previously known to be related with increased risk of CRC. We retrospectively evaluated the data of 741 consecutive Caucasian patients with T2DM who underwent colonoscopic screening in our tertiary referral center. A control cohort of 333 patients with thyroid disease was selected to evaluate the difference in the incidence of CRC. At a median follow-up of 132.5 months (range 33.3-175.7), 67 cases of cancer (prevalence 9%) occurred; among these, 14 cases of CRC were reported (prevalence 1.88%) among the diabetic patients, while only two case (one of these was a CRC) (overall prevalence 0.006%, prevalence of CRC 0.003%) occurred in the control group; the difference between the prevalence of CRC was statistically significant (chi-square 4.21, p=0.04). The median duration of T2DM to CRC diagnosis was 168 months (range 12-768). At the univariate analysis, older age (p=0.001, r 0.138) and diabetes duration (p=0.001, r 0.138) were related to higher risk of cancer, while metformin seems to be protective towards cancer (p=0.07, r -0.098). In the subset of patients with CRC, the age (RR = 2.25; 95% CI: 0.30 - 17.31; p < 0.001), the diabetes duration (RR = 1.93; 95% CI: 0.25 – 14.77; p = 0.001) and the sulphonylureas treatment (RR = 2.33; 95% CI: 0.78 – 7.38; p = 0.007) were independently correlated with CRC. In our study, the prevalence of CRC in the cohort of patients with T2DM was higher compared to that from the National Tumor Register in 2010 (0.5%). Furthermore, we could speculate that sulphonylureas may play a role in CRC carcinogenesis impairing the physiological insulin secretion.

Key words: type 2 diabetes, colorectal cancer, anti-diabetic drugs

Mailing address:
Dr. Emanuele Sinagra,
Gastroenterology and Endoscopy Unit,
Fondazione Istituto Giuseppe Giglio,
Contrada Pietra Pollastra Pisciotto, 90015 Cefalù, Italy
Tel.: +39 921920712 - Fax: +39 921920406
e-mail: emanuelesinagra83@googlemail.com

0393-974X (2017)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

To the Editor,

Colorectal cancer (CRC) is the most common malignancy of the gastrointestinal tract (1, 2). The incidence of CRC increased during the last two decades, even though there were many strategies for prevention.

On the other hand, the prevalence of diabetes mellitus (DM) has increased significantly over the past several decades, mostly due to the growing epidemic of obesity. Approximately 8% of the US population has DM, classified as type 2 DM (T2DM) in more than 90% of cases, with insulin resistance as the main underlying pathophysiological cause (3).

CRC and DM, share several risk factors including high caloric diet, obesity, hyperinsulinemia, cigarette smoking and physical inactivity. Hyperinsulinemia may promote colorectal carcinogenesis through a cross-talk with the insulin-like growth factor-1 (IGF-1) receptor, which stimulates proliferation and prolongs cell survival (4). A stimulatory effect on cell growth of intestinal epithelial and colon cancer cells was shown in preclinical studies (5, 6). In addition, hyperinsulinemia was also associated with increased tumor growth in *in vivo* experiments (7).

Many studies have reported a positive association between T2DM and CRC (8, 9), even though others have not reported any association (10, 11).

The aim of the current study is to evaluate the prevalence of CRC in a cohort of Caucasian patients with T2DM and the potential factors associated with the risk of CRC in patients with T2DM.

MATERIALS AND METHODS

We retrospectively studied the data of 741 patients (381 M, 360 F; mean age 67±9.6 years) with T2DM, without any gastrointestinal symptoms, who underwent colonoscopic screening for colorectal cancer, consecutively admitted to the Section of Endocrinology of the University of Palermo from January 2000 to December 2008. Three hundred and thirty-three subjects matched for gender (145 M, 188 F) and age (64±9 years) were enrolled among patients with thyroid disease as controls. Diabetic patients were on treatment with insulin in 310 cases, metformin in 485, sulphonylureas in 68, glinides in 263, while 115 patients were on other hypoglycemic drugs.

The exclusion criteria included a history of colonic disease, such as colitis, polyps, or cancer, prior colonic surgery or colon polypectomy, or medical history of severe hematologic or connective disorders.

The reason why colonoscopy instead of fecal occult blood test and sigmoidoscopy was chosen is that flexible sigmoidoscopy can only identify lesions in the distal 60 cm of the bowel and abnormal findings in the distal bowel require colonoscopy for visualization of the entire colon. On the other hand, colonoscopic examination showed the highest effectiveness for screening colon cancer (12), because the procedure can show the entire colon and lesions can be removed at the same time.

The diagnosis of T2DM was made according to the American Diabetes Association guidelines (13).

Data were collected from baseline until the end of the observation period (2008). Body mass index (BMI), alcohol and non steroideal anti-inflammatory drug (NSAID) consumption, smoking, family history of CRC, HbA1c levels, patient comorbidities (hypertension, hypertriglyceridemia, obesity), age at diabetes onset and duration of diabetes, treatment with insulin or other hypoglycemic drugs at the diagnosis, were from patient charts.

Statistical analysis

Data were collected in Microsoft Excel and imported into the PASW Statistics 18.0 for Windows (SPSS Inc., IL, USA) for statistical analysis. The normality of quantitative variables was tested with the Shapiro-Wilk test. Baseline characteristics were presented as mean ± SD for continuous variables; rates and proportions were calculated for categorical data. Differences between the two groups were detected using the unpaired Student's t-test for continuous variables (after testing for equality of variance: Levene test) and the $\chi 2$-test and Fisher's exact test (when appropriate) for categorical variables. Simple univariate correlations among continuous variables with non-normal distribution were determined by Pearson's test. Variables associated with the dependent variable on univariate analysis (probability threshold, $p \leq 0.10$) were included in two multivariate regression models. In both models, the following independent variables were included: age and diabetes duration as continuous variables. In the first model, smoking, metformin and sulphonylureas

treatment were included as categorical variables. In the second model, gender and metformin treatment were included as categorical variables. A two-sided p value < 0.05 was considered statistically significant.

RESULTS

Clinical and demographic data of patients are summarized in Table I. Diabetic patients represented 68.9% of the study population [mean age at DM onset 51.2±11.1 years; median duration of disease 168 months (range 12-768)]. The mean BMI was 29.9±5.4 kg/m^2 and mean blood glycated hemoglobin level was 7.6±1.4%. Hypertension was found in 81.2% of patients and hypertriglyceridemia in 40.8%.

The control group represented 31.1% of the study population. The mean age at thyroid disease onset was 50±11 years, and the median duration of thyroid disease was 98 months (range 12-180).

At a median follow-up of 132.5 months (range 33.3-175.7), 67 cases of cancer (prevalence 9%) occurred in the entire diabetic population, while in the control group only 2 patients had cancer (overall cancer prevalence 0.006%). Fourteen cases of CRC were reported (prevalence 1.88%) among diabetic patients (Table II), while only one was reported in the control group (prevalence 0.003%). The difference between the groups was statistically significant (*chi*-squared 4.21, p=0.04) (data not shown). The median duration of DM to CRC diagnosis was 156 months (range 1-768).

In patients with diabetes, at the univariate analysis, age (p=0.001, r 0.138) and diabetes duration (p=0.001, r 0.138) were found to be correlated

Table I. *Baseline features of diabetic patients and control group.*

Variables	Diabetic patients (N=741)	Control group (N=333)
	Mean ± SD	**Mean ± SD**
Age (years)	67±9.6	64±9
Age at diabetes onset (years)	51.2±11.1	NA
Body mass index (Kg/m^2)	29.9±5.4	27±4.7
Glycated hemoglobin (%)	7.6±1.4	NA
	Subjects (%)	**Subjects (%)**
Gender: Male Female	381 (51.4%) 360 (48.6%)	145 (43.5%) 188 (56.5%)
Smokers	189 (25.5%)	35 (10.5%)
Alcohol consumption	4 (0.005%)	2 (0.006%)
Non-steroideal antiinflammatory drug consumption	306 (41.2%)	5 (0.01%)
Family history of colorectal cancer	13 (0.02%)	5 (0.01%)
Diabetes treatment		
Sulphonylureas	68 (0.09%)	0 (0)
Glinides	263 (35.4%)	0 (0)
Metformin	485 (65.4%)	0 (0)
Insulin	310 (41.8%)	0 (0)
Others	115 (15.5%)	0 (0)
Comorbidities		
Hypertension	602 (81.2%)	103 (30.9%)
Hypertriglyceridemia	302 (40.7%)	81 (24.3%)

Table II. *Malignant cancer cases and their distribution by type in diabetic patients and controls.*

Type of cancer	Diabetic patients (N= 741)	Controls (N=333)
	Subjects (%)	Subjects (%)
Total	67 (9%)	2 (0.6%)
Colorectal cancer	14 (1.8%)	1 (0.3%)
Breast cancer	15 (4.1%)	1 (0.3%)
Lymphomas	6 (0.8%)	0
Bladder cancer	6 (0.8%)	0
Cancer of uterus	5 (1.38%)	0
Prostatic cancer	5 (1.38%)	0
Papillary thyroid cancer	4 (0.54%)	0
Non-melanoma skin cancer	3 (0.4%)	0
Pancreatic cancer	2 (0.27%)	0
Hepatocellular carcinoma	2 (0.27%)	0
Penile cancer	1 (0.13%)	0
Lung cancer	1 (0.13%)	0
Ovarian cancer	1 (0.13%)	0
Larynx cancer	1 (0.13%)	0
Renal cancer	1 (0.13)	0

with CRC. As expected, metformin appeared to be protective towards cancer (p=0.07, r -0.98) (Table III). Data were further analyzed using two binary logistic regression models (Table III). Among all independent variables examined, the age (RR = 2.25; 95% CI: 0.30 - 17.31; p < 0.001), the diabetes duration (RR = 1.93; 95% CI: 0.25 – 14.77; p = 0.001) and the sulphonylureas treatment (RR = 2.33; 95% CI: 0.78 – 7.38; p = 0.007) were independently correlated with CRC (Table III). An inverse independent association was found for metformin treatment (RR = 0.32; 95% CI: 0.13 – 0.76; p = 0.005) (Table III).

With regard to other tumors (not including CRC), age (RR = 1.04; 95% CI: 1.02 – 1.05; p = 0.007) and diabetes duration (RR = 1.07; 95% CI: 0.24 – 4.69; p = 0.005) showed an independent association, while metformin treatment showed an inverse independent association (RR = 0.44; 95% CI: 0.19 – 0.98; p = 0.009) (Table IV).

DISCUSSION

Epidemiological studies on the association between T2DM and risk of CRC are scarce and inconclusive. The results of the current study demonstrated that overall cancer prevalence, and in detail the CRC prevalence, was higher in diabetic patients than in the control group and this prevalence was also higher than that reported in the Italian tumor registry (15), supporting the results of several epidemiological studies and meta-analyses (8, 16, 17).

In the univariate analysis, we found a correlation between CRC and age or diabetes duration, suggesting that age and diabetes duration are independent factors influencing CRC. Metformin was found to be a protective factor for overall malignant neoplasms, even though this correlation was not found for CRC. The finding of the current study that treatment with sulphonylureas increased the CRC risk (p=0.001),

Table III. *Univariate and multivariate analysis (logistic regression model) of risk factors associated with colon cancer in patients with and without diabetes.*

Variable	Patients with diabetes and colon cancer (N=14)	Patients with diabetes without colon cancer (N=727)	Univariate analysis	Multivariate Analysis	
	Mean ± SD	Mean ± SD	*p*	RR (95% CI)	*p*
Age (years)	74.81±9.21	66.81±9.52	<0.001	2.25 (0.303-17.317)	<0.001
Body Mass Index (kg/m^2)	30.27±3.69	29.9±5.45	0.501		
Diabetes duration (months)	230.21±168.6	168.05±115.5	0.013	1.93 (0.258-14.778)	0.001
Glycated haemoglobin (%)	7.55±1.79	7.56±1.42	0.680		
	Subjects (%)	Subjects (%)			
Gender Male Female	 8 (57.1%) 6 (42.8%)	 369 (50.7%) 358 (49.3%)	 0.665		
Smoking	9 (64.2%)	261 (35.9%)	0.087	1.24 (0.548-3.172)	0.325
Alcohol consumption	0	5 (0.68%)	0.780		
Non-steroideal anti-inflammatory drugs consumption	6 (42.8%)	300 (41.2%)	0.626		
Family history of cancer	1 (7.14%)	11 (16.1%)	0.480		
Diabetes treatment					
Insulin treatment	7 (50%)	299 (41.1%)	0.980		
Metformin treatment	5 (35.7%)	477 (65.6%)	0.007	0.32 (0.128-0.767)	0.005
Sulphonylureas treatment	4 (28.5%)	64 (8.8%)	0.001	2.32 (0.788-7.384)	0.007
Glinides treatment	4 (28.5%)	257 (35.3%)	0.980		
Comorbidities					
Hypertension	10 (71.4%)	587 (80.7%)	0.330		
Hypertriglyceridemia	6 (42.8%)	295 (40.5%)	0.781		
Hypo-HDL	7 (50%)	288 (39.6%)	0.121		

but not the insulin treatment, may exclude an adverse property of the insulin formulation itself. We believe that the strength of the study is the evaluation of many parameters as crucial factors associated with CRC and the finding of increased prevalence of CRC in diabetic patients compared to the Italian reported prevalence. However, some study limitations should be considered. The study has a retrospective design, and the control group is quite small. With regards to the control group, we included patients with thyroid disease, even though the role of clinical hypothyroidism or hyperthyroidism in cancer growth is under investigation (18).

Therefore, the effect of anti-diabetic drugs in the carcinogenesis and the factors involved in the CRC need to be further investigated. Prospective case-control studies are required to evaluate better the long-term safety of anti-diabetic drugs.

Table IV. *Univariate and multivariate analysis (logistic regression model) of risk factors associated with other malignant tumors (excluding colon cancer) in patients with and without diabetes.*

Variable	Patients with diabetes and other tumors (N= 53)	Patients with diabetes without other tumors (N= 688)	Univariate analysis	Multivariate Analysis	
	Mean ± SD	Mean ± SD	*p*	RR (95% CI)	*p*
Age (years)	71.02±7.39	66.72±9.69	0.001	1.04 (1.023-1.056)	0.007
Body mass index (kg/m^2)	29.28±4.81	29.97±5.46	0.510		
Diabetes duration (months)	203.32±128.4	168.29±116.7	0.030	1.07 (0.247-4.690)	0.005
Glycated haemoglobin (%)	7.50±1.29	7.55±1.44	0.830		
	Subjects (%)	Subjects (%)			
Gender Male Female	 22 (41.5%) 31 (58.5%)	 357 (51.9%) 331 (48.1%)	 0.043	 0.91 (0.484-2.464)	 0.440
Smoking	18 (34%)	250 (36.3%)	0.722		
Alcohol consumption	0	5 (0.72%)	0.560		
Non-steroidal anti-inflammatory drug consumption	18 (34%)	288 (41.8%)	0.081		
Family history of cancer	1 (1.9%)	11 (1.6%)	0.570		
Diabetes treatment					
Insulin treatment	25 (47.2%)	282 (40.9%)	0.129		
Metformin treatment	30 (56.6%)	452 (65.6%)	0.050	0.44 (0.192-0.985)	0.009
Sulphonylureas treatment	5 (9.4%)	63 (9.1%)	0.370		
Glinides treatment	17 (32.1%)	245 (35.6%)	0.881		
Comorbidities					
Hypertension	45 (84.9%)	555 (80.6%)	0.607		
Hypertriglyceridemia	22 (41.5%)	280 (41.9%)	0.880		
Hypo-HDL	20 (37.7%)	278 (41.6%)	0.680		

Nevertheless, despite our study showing the above-mentioned methodological limits, we should take into consideration that, given that high prevalence of diabetes, even a small increase of CRC risk may have important public health implications and a CRC screening of patients with diabetes may be required.

REFERENCES

1. Omran S, Ismail AA. Knowledge and beliefs of Jordanians toward colorectal cancer screening. Cancer Nurs 2010; 33:141-48.
2. Sinagra E, Raimondo D, Gallo E, et al. Could JC virus provoke metastasis in colon cancer? World J Gastroenterol 2014; 20:15745-49.
3. Centers for Disease Control and Prevention: National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, US Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
4. Pollak M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. Nat Rev Cancer 2012; 12:159-69.
5. Koenuma M, Yamori T, Tsuruo T. Insulin and insulin-like growth factor 1 stimulate proliferation of metastatic variants of colon carcinoma 26. Jpn J Cancer Res 1989; 80:51-58.
6. Björk J, Nilsson J, Hultcrantz R, Johansson C. Growth-regulatory effects of sensory neuropeptides, epidermal growth factor, insulin, and somatostatin on the non-transformed intestinal epithelial cell line IEC-6 and the colon cancer cell line HT 29. Scand J Gastroenterol 1993;28:879-84.
7. Tran TT, Medline A, Bruce WR. Insulin promotion of colon tumors in rats. Cancer Epidemiol Biomarkers Prev 1996; 5:1013-15.
8. Larsson SC, Giovannucci E, Wolk A. Diabetes and colorectal cancer incidence in the cohort of Swedish men. Diabetes Care 2005; 28:1805-7.
9. Deng L, Gui Z, Zhao L, Wang J, Shen L. Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. Dig Dis Sci 2012; 57:1576-85.
10. Limburg PJ, Vierkant RA, Fredriksen ZS, et al. Clinically confirmed type 2 diabetes mellitus and colorectal cancer risk: a population-based, retrospective cohort study. Am J Gastroenterol 2006; 101:1872-79.
11. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006; 166:1871-77.
12. Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutritional Study I Follow-up data: diabetes, cholesterol, pulse, and physical activity. Cancer Epidemiol Biomarkers Prev 1995; 4:807-11.
13. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008; 58:130-60.
14. American Diabetes Association. Standards of medical care in diabetes – 2017. Diabetes Care 2017; 40 (S 1):1-142.
15. AIRTUM Working Group. I tumori in Italia, rapporto 2010. La prevalenza dei tumori in Italia. Epidemiol Prev 2010; 34:1-148.
16. L, Gui Z, Zhao L, Wang J, Shen L. Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. Dig Dis Sci 2012; 57:1576-85.
17. Sun L, Su Y. Diabetes mellitus is an independent risk factor for colorectal cancer. Dig Dis Sci 2012; 57:1586-97.
18. Lin HY, Chin YT, Yang YC, et al. Thyroid Hormone, Cancer, and Apoptosis. Compr Physiol 2016; 6:1221-37.